

REMARKSInformation Disclosure Statement

Applicants direct the Examiner's attention to the Information Disclosure Statement (IDS) being filed concurrently herewith.

Priority

The Examiner acknowledges Applicant's claim for foreign priority based on an application filed in Denmark on July 4, 1995 and a PCT application filed July 3, 1996, but notes that Applicant "has not filed a certified copy of the priority applications as required by 35 U.S.C. 119(b)" (Office Action, page 3).

Applicants are filing concurrently herewith certified copies of DK 0782/95 filed July 4, 1995 and PCT/EP96/02926 filed July 3, 1996, thereby perfecting the claim for priority.

Objection to the Amendment under 35 U.S.C. §132

The Amendment filed February 27, 1999 is objected to under 35 U.S.C. §132 "because it introduces new matter into the disclosure" (Office Action, page 3). The Examiner states that the material which is not supported by the original disclosure is "wherein the site of the naturally occurring deletion is not site III".

Applicants respectfully disagree. The addition of a proviso does not raise a *per se* presumption that new matter is added. Ex parte Parks, 30 U.S.P.Q. 90, 96 (C.C.P.A. 1976). The subject matter of the claim need not be described literally (i.e., word for word) in order for the disclosure to satisfy the description requirement. In re Wertheim, 191 U.S.P.Q. 90,96 (C.C.P.A. 1976). See also M.P.E.P. §2163.02. Description can be found in the teachings taken as a whole.

The Court of Customs and Patent Appeals has stated that:

[W]e must decide whether the invention appellants seek to protect by their claims is part of the invention that appellants have described *as theirs* in the specification. That what appellants claim as patentable to them is *less* than what they describe as their invention is not conclusive if their specification also reasonably describes that which they do claim. Inventions are constantly made which turn out not to be patentable, and applicants frequently discover during the course of prosecution that only a part of what they invented and originally claimed is patentable. . . . To rule otherwise would let form triumph over substance, substantially eliminating the right of an applicant to retreat to an otherwise patentable species merely because he erroneously thought he was first with the genus when he filed. (Emphasis in original). In re Wertheim at 97.

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In In re Johnson and Farnham, 194 U.S.P.Q. 187 (C.C.P.A. 1977), the court found that Appellants' exclusion of two species from an original genus claim to avoid having the claims read on a lost interference count was supported by the specification. The application mentioned by name fifty specific precursor compounds, E, and a description of an E' precursor as well as 26 examples of 15 species of polyarylene polyethers formed from E and E'.

The pertinent portion of the claims in question read:

... with the provisos that E and E' may not both include a divalent sulfone group and may not both include a divalent carbonyl group linking two aromatic groups. (Emphasis in original). Id. at 191.

The court stated that:

... Appellants ... are narrowing their claims, and the full scope of the limited genus now claimed is supported in appellants' earlier application, generically and by specific examples.

The notion that one who fully discloses, and teaches those skilled in the art how to make and use, a genus and numerous species therewithin, has somehow failed to disclose, and teach those skilled in the art how to make and use, that genus minus two of those species, and has thus failed to satisfy the requirements of § 112, first paragraph, appears to result from a hypertechnical application of legalistic prose relating to that provision of the statute. Id. at 196.

In the instant specification, Applicants teach that the MVA genome has six major deletions and that the invention is drawn to a "recombinant virus containing and capable of expressing at least one foreign gene inserted at the site of a naturally occurring deletion within the MVA genome" (specification, page 5, lines 15-16; page 7, lines 4-6). Applicants describe how to construct the claimed recombinant MVA viruses and provide specific examples of a recombinant MVA virus which allows expression of the HIV-1 nef gene under control of the vaccinia virus early/late promoter P7.5 and a recombinant MVA virus which allows expression of the human tyrosinase gene under control of the vaccinia virus early/late promoter P7.5 (see specification, pages 25-37).

Accordingly, a person skilled in the art would recognize from the specification, as originally filed, that Appellants had possession of the presently claimed recombinant MVA viruses at the time the subject application was filed. Thus, the proviso is clearly supported by the original disclosure.

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Objection to Claims 4-7

The Examiner states that "Claims 4 and 5 recite improper Markush language" (Office Action, page 4).

The Examiner states that Claim 4 uses too many "or" clauses. As amended, Claim 4 is directed a proper Markush claim.

The Examiner states that Claim 6 has a typographical error. Claim 6 has been amended to correct the typographical error.

Rejection of Claims 1-11 and 31-34 under 35 U.S.C. §112, second paragraph

Claims 1-11 and 31-34 are rejected under 35 U.S.C. §112, second paragraph "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention" (Office Action, page 4).

The Examiner states that the "claims recite a variety of abbreviations such as MVA, HIV, and TYR" and that the abbreviations should be spelled out at their first appearance in the claims" (Office Action, page 4). As amended the claims include the full spelling of the abbreviations.

The Examiner states that "Claim 11 is vague and indefinite as it is not clear whether Applicant intends the recombinant virus to be able to replicate in human cells, or whether the virus is to be free of virus which can replicate in human cells" (Office Action, page 4). As amended, Claim 11 is directed to recombinant Modified Vaccinia Ankara (MVA) viruses according to Claim 1 wherein the viruses cannot replicate in human cells.

Rejection of Claims 1-11 under 35 U.S.C. §112, first paragraph

Claims 1-11 are rejected under 35 U.S.C. §112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor (s), at the time the application was filed, had possession of the claimed invention" (Office Action, page 5). The Examiner states that the "whole of the specification is directed to recombinant MVA viruses wherein the insertion is at site II" and that there "is no direct teaching that excludes insertions at site III, nor any reasons why one would exclude such insertions" (Office Action, page 5). The Examiner states that the amendment to Claim 1 "is new matter, and must be canceled in response to this rejection" (Office Action, page 5).

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Applicants respectfully disagree. As discussed above, the addition of a proviso does not raise a *per se* presumption that new matter is added. Ex parte Parks, 30 U.S.P.Q. 90, 96 (C.C.P.A. 1976). The subject matter of the claim need not be described literally (i.e., word for word) in order for the disclosure to satisfy the description requirement. In re Wertheim, 191 U.S.P.Q. 90,96 (C.C.P.A. 1976). See also M.P.E.P. §2163.02. Description can be found in the teachings taken as a whole.

The Court of Customs and Patent Appeals has stated that:

[W]e must decide whether the invention appellants seek to protect by their claims is part of the invention that appellants have described *as theirs* in the specification. That what appellants claim as patentable to them is *less* than what they describe as their invention is not conclusive if their specification also reasonably describes that which they do claim. Inventions are constantly made which turn out not to be patentable, and applicants frequently discover during the course of prosecution that only a part of what they invented and originally claimed is patentable. . . . To rule otherwise would let form triumph over substance, substantially eliminating the right of an applicant to retreat to an otherwise patentable species merely because he erroneously thought he was first with the genus when he filed. (Emphasis in original). In re Wertheim at 97.

In In re Johnson and Farnham, 194 U.S.P.Q. 187 (C.C.P.A. 1977), the court found that Appellants' exclusion of two species from an original genus claim to avoid having the claims read on a lost interference count was supported by the specification. The application mentioned by name fifty specific precursor compounds, E, and a description of an E' precursor as well as 26 examples of 15 species of polyarylene polyethers formed from E and E'.

The pertinent portion of the claims in question read:

. . . with the provisos that E and E' may not both include a divalent sulfone group and may not both include a divalent carbonyl group linking two aromatic groups. (Emphasis in original). Id. at 191.

The court stated that:

. . . Appellants . . . are narrowing their claims, and the full scope of the limited genus now claimed is supported in appellants' earlier application, generically and by specific examples.

The notion that one who fully discloses, and teaches those skilled in the art how to make and use, a genus and numerous species therewithin, has somehow failed to disclose, and teach those skilled in the art how to make and use, that genus minus two of those species, and has thus failed to satisfy the requirements

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of § 112, first paragraph, appears to result from a hypertechnical application of legalistic prose relating to that provision of the statute. *Id.* at 196.

In the instant specification, Applicants teach that the MVA genome has six major deletions and that the invention is drawn to a “recombinant virus containing and capable of expressing at least one foreign gene inserted at the site of a naturally occurring deletion within the MVA genome” (specification, page 5, lines 15-16; page 7, lines 4-6). Applicants also describe construction of the claimed recombinant MVA viruses and provide specific examples of the claimed recombinant MVA virus which allows expression of the HIV-1 nef gene under control of the vaccinia virus early/late promoter P7.5 and which allows expression of the human tyrosinase gene under control of the vaccinia virus early/late promoter P7.5 (see specification, pages 25-37).

Accordingly, a person skilled in the art would recognize from the specification, as originally filed, that Appellants had possession of the presently claimed recombinant MVA viruses at the time the subject application was filed. Thus, the specification sufficiently describes the claimed invention and Applicants have satisfied the requirements under 35 U.S.C. §112.

Rejection of Claims 1-3 and 8-11 under 35 U.S.C. §102(a)

Claims 1-3 and 8-11 are rejected under 35 U.S.C. §102(a) “as being anticipated by Sutter et al.” (Office Action, page 5). The Examiner states that “[p]erfection of Applicant’s claim to foreign priority would obviate the rejection” (Office Action, page 5).

As indicated above, Applicants are filing concurrently herewith certified copies of DK 0782/95 filed July 4, 1995 and PCT/EP96/02926 filed July 3, 1996, which perfects the claim for priority. Thus, the rejection under 35 U.S.C. §102(a) has been obviated.

Rejection of Claims 1-5 and 11 under 35 U.S.C. §103(a)

Claims 1-5 and 11 are rejected under 35 U.S.C. §103(a) “as being unpatentable over Small Jr. et al. (US Patent 5,676,950)” (Office Action, page 6). The Examiner states that Small et al. disclose “recombinant MVA viruses wherein antigenic determinants from influenza or from HIV are inserted into a naturally occurring deletion of the MVA virus” (Office Action, pages 6-7). The Examiner notes that Small et al. “do not specifically identify which insertion is used in their recombinant viruses” (Office Action, page 7). It is the Examiner’s opinion that:

[i]t would have been obvious for one of ordinary skill in the art at the time the invention was made to have selected any one of the naturally occurring deletion

sites of MVA for insertion of sequences encoding heterologous antigens. Small Jr. et al. disclose that MVA has six suitable sites for such insertions, and indicates that any site can be utilized. Heterologous antigens are efficiently expressed from the insertion sites, and such antigens can provide protection from homologous challenges. Small Jr. et al. disclose the suitability of several antigens for such expression, including antigens of viruses, bacteria and parasites. One would have been motivated to use MVA virus because it is an excellent vaccine candidate due to its extreme attenuation, the availability of insertion sites, the level of gene expression, and the safety for laboratory workers (Office Action, page 7).

Applicants respectfully disagree. In particular, Applicants disagree that Small *et al.* "disclose that MVA has six suitable sites *for such insertions*, and *indicates that any site can be utilized*" (Office Action, page 7, emphasis added), and respectfully request that the Examiner direct Applicants' attention to such a teaching in the Small *et al.* patent.

An obviousness rejection requires both (1) that "the prior art would have suggested to the person of ordinary skill in the art that they should . . . carry out the claimed process"; and (2) that the prior art should establish a reasonable expectation of success. *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in applicant's disclosure." *Id.*

Applicants' claimed invention is directed to a recombinant MVA virus containing and capable of expressing at least one foreign antigen inserted at a site of a naturally occurring deletion within the MVA genome, wherein the site of the naturally occurring deletion is not site III. Applicants teach that the MVA genome has six major deletions and that the invention is drawn to a "recombinant virus containing and capable of expressing at least one foreign gene inserted at the site of a naturally occurring deletion within the MVA genome" (specification, page 5, lines 15-16; page 7, lines 4-6). Applicants also describe construction of the claimed recombinant MVA viruses and provide specific examples of the claimed recombinant MVA virus which allows expression of the HIV-1 nef gene under control of the vaccinia virus early/late promoter P7.5 and which allows expression of the human tyrosinase gene under control of the vaccinia virus early/late promoter P7.5 (see specification, pages 25-37).

Small *et al.* administered MVA HA-NP to mice which demonstrated the "potential immunogenicity and efficacy of MVA HA-NP as an oral vaccine" (Small *et al.*, column 6, lines 63-64, Example 6). Small *et al.* do not specifically disclose how the MVA HA-NP was constructed, but do cite Sutter *et al.* 1994 (Reference AR, PTO form 1449). Sutter *et al.* describe plasmids in which the hemagglutinin (HA) and nucleoprotein (NP) genes are inserted into the

deletion site III of the MVA virus (Sutter *et al.*, page 1032, column 2; Figure 1). Small *et al.* note the "six major deletions" in the MVA genome (Sutter *et al.*, column 6, line 16). Small *et al.*, however, do not teach or even suggest that a foreign gene could be inserted into any naturally occurring deletion site, other than site III, within the MVA genome and expressed, and thus, do not provide a reasonable expectation of doing so.

The major deletion sites of MVA occurred because they were superfluous regions within the genome of the MVA virus, i.e., not necessary for replication and generation of new MVA viruses. Foreign genes integrated into the MVA genome are also superfluous. A person of skill in the art would have expected that insertion of foreign genes into the MVA deletion sites would have resulted in deletion of the foreign genes as well. Furthermore, the deletions in the MVA genome generated new protein coding sequences, referred to as Open Reading Frames (ORFs). These newly created ORFs are important for replication and genome stability of the MVA virus. It is assumed that these sequences encode a variety of proteins which interact with the host cell. Such DNA sequences, referred to as cis-acting elements, are necessary to reprogram host cells for viral replication and packaging of the viral genome into infectious particles. Accordingly, a person of skill in the art would have expected that integration of foreign sequences into one or more of the deletion sites, which are assumed to include these cis-acting elements, would compromise the life cycle of the MVA virus. Sutter *et al.* did find that deletion site III of the MVA virus can be used to insert a heterologous gene for expression, however, a teaching that deletion site III of the MVA virus can be used for insertion and expression of foreign genes in no way indicates that other deletion sites in the MVA genome can be used similarly. Indeed, neither Small *et al.* nor Sutter *et al.* suggest that this is even a possibility.

Without knowledge of the teaching of the present invention a skilled practitioner would have expected that insertion of heterologous sequences into any other deletion site of the MVA viral genome would be unstable or result in rearrangement of the inserted sequences. The teachings in the prior art only direct a person of skill to use the deletion site III of the MVA virus for insertion and expression of heterologous sequences.

In summary, Small *et al.* do not teach or even suggest that a foreign gene could be inserted into any naturally occurring deletion site, other than site III, within the MVA genome for expression. Thus, the teachings of Small *et al.* do not render obvious the subject matter of Applicants' claimed invention.

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Rejection of Claims 6, 7, 31 and 32 under 35 U.S.C. §103(a)

Claims 6, 7, 31 and 32 are rejected under 35 U.S.C. §103(a) “as being unpatentable over Small Jr. et al. (US Patent 5,676,950) as applied to claims 1-5 and 11 above, in view of Altenburger et al. (1989 PTO-1449 AZ) and further in view of Montagnier et al. (US Patent 5,221,610)” (Office Action, page 8). The Examiner states that “Altenburger *et al.* disclose recombinant MVA viruses and the location of deletion II” and suggest that “MVA recombinants can express malaria antigens from genes inserted into this location” (Office Action, pages 8-9). The Examiner further states that Altenburger *et al.* note that “recombinant MVA viruses having insertions into the deletion II area could potentially be used as vaccines” and provide “motivation to insert foreign gene of interest into the deletion II region of MVA, in order to obtain foreign gene expression” (Office Action, page 9). The Examiner states that Montagnier *et al.* teach the HIV nef protein, and nucleotides encoding nef, for use in producing recombinant nef polypeptides which can be used in HIV detection, and in immunogenic compositions” (Office Action, page 9). The Examiner further states that Montagnier *et al.* express the nef protein from recombinant vaccinia viruses” (Office Action, page 9). It is the Examiner’s opinion that:

[i]t would have been obvious for one of ordinary skill in the art at the time the invention was made to have selected any one of the naturally occurring deletion sites of MVA, including site II, for insertion of sequences encoding heterologous antigens. Small, Jr. et al. disclose that MVA has six suitable sites for such insertions, and indicate that any site can be utilized. Both Altenburger et al. and Small Jr. et al. disclose that heterologous antigens are efficiently expressed from the insertion sites, and such antigens can provide protection from homologous challenge. Small Jr. et al. disclose the suitability of several antigens for such expression, including antigens of HIV for use in recombinant MVA viruses. One of skill in the art would have been motivated to select the nef gene of HIV in view of the disclosure of Montagnier et al. which indicates that immunogens comprising nef proteins are highly desirable for vaccine compositions against AIDS. One of skill in the art would have been further motivated to use the MVA virus because it is an excellent vaccine candidate due to its extreme attenuation, the availability of insertion sites, the level of gene expression, and the safety for laboratory workers (Office Action, page 9-10).

As discussed above, Small *et al.* do not teach or even suggest that a foreign gene could be inserted into any naturally occurring deletion site, other than site III, within the MVA genome and expressed. Furthermore, Applicants respectfully disagree that Altenburger *et al.* suggest that “MVA recombinants can express malaria antigens from genes inserted into” deletion site II of the MVA genome (Office Action, pages 8-9). Altenburger *et al.* do not teach or even suggest that a foreign gene could be inserted into deletion site II of the MVA genome and expressed.

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Applicants respectfully submit that this rejection is improper because the Examiner has not identified a suggestion in the prior art of the desirability of the proposed combination of references. Combining the elements of separate references which do not themselves suggest the combination necessary to obtain a claimed invention is generally improper. ACS Hospital Systems, Inc. v. Montefiore Hospital, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984). The only document of record which suggests the desirability of the proposed combination is Applicants' specification. However, the use of the present specification as an instruction manual or template to piece together the teachings of the prior art is impermissible hindsight. A *prima facie* case of obviousness is established only if the teachings of the cited art would have suggested the claimed invention to one of ordinary skill in the art with a reasonable expectation of successfully achieving the claimed results. In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be found in the prior art, not Applicants' disclosure. Id.

The Court of Appeals for the Federal Circuit has stated that "[t]he proper approach to the obviousness issue must start with the claimed invention *as a whole*." See, e.g., Kimberley-Clark Corp. v. Johnson & Johnson Co., 223 U.S.P.Q. 603, 609 (Fed. Cir. 1984). See also Lindemann Maschinenfabrik G.m.b.H. v. American Hoist & Derrick Co., 221 U.S.P.Q. 481, 488 (Fed. Cir. 1984). It is not proper to pick and choose among individual elements of assorted prior art references to recreate the claimed invention. Smithkline Diagnostics Inc. v. Helena Laboratories Corp., 8 U.S.P.Q.2d 1468, 1475 (Fed. Cir. 1988); Akzo N.V. v. International Trade Comm., 11 U.S.P.Q.2d 1241, 1246 (Fed. Cir. 1986).

The claimed invention relates to a recombinant MVA virus containing and capable of expressing HIV nef or human tyrosinase inserted at a site of a naturally occurring deletion within the MVA genome, wherein the site of the naturally occurring deletion is not site III.

None of the cited references, either alone or in combination, would have suggested the claimed invention to one of ordinary skill in the art at the time the invention was made with a reasonable expectation of success. As discussed above, Small *et al.* do not teach or even suggest that a foreign gene could be inserted into any naturally occurring deletion site, other than site III, within the MVA genome for expression. Accordingly, Small *et al.* do not teach or suggest the recombinant MVA viruses of Claims 6, 7, 31 and 32.

The additional teachings of the Altenburger *et al.* reference and the Montagnier *et al.* patent do not cure the deficiencies of the Small *et al.* patent. Altenburger *et al.* analyzed the first

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and second deletion sites of the MVA virus which are located at the terminal fragment of the MVA genome. Altenburger *et al.* do not teach or even suggest that a foreign gene could be inserted into deletion site II of the MVA genome and expressed. Furthermore, both terminal regions undergo complex sequence rearrangements during cell culture propagation. Thus, when inserting heterologous genes into deletion sites located in the terminal regions of the MVA genome, one of skill in the art would not expect expression of the heterologous sequence due to deletions or rearrangements of the inserted sequence.

The Examiner refers Applicant to page 25, paragraph 2 of the Altenburger *et al.* reference. In that passage Altenburger *et al.* states that:

[i]n the MVA virus this second deletion eliminated more than two thirds of the presumptive human host range. In spite of this, clinical vaccination trials [30] and our in vitro experiments strongly suggest that the MVA virus is able to replicate in certain human cells. Moreover, human 143 B TK-cells support the replication of MVA recombinant expressing malaria antigens.

However, as evidenced in the following paragraph, Altenburger *et al.* refers to "MVA tk-recombinants". There is no discussion in the Altenburger *et al.* reference regarding the insertion of a heterologous gene in deletion site II of the MVA genome.

Montagnier *et al.* teach "[p]olypeptides encoded by the nef gene of Human Immunodeficiency Virus (HIV)" (Montagnier *et al.*, abstract). Montagnier *et al.* further teach that the "nef protein can be obtained by expression of a sequence coding for the protein in vaccinia virus" (Montagnier *et al.*, column 13, lines 15-16). There is no discussion of the MVA virus in the Montagnier *et al.* patent.

A combination of the cited art would at most direct the person of skill in the art to construct a recombinant vaccinia virus which expresses the nef protein for oral immunization, or construct a recombinant MVA virus in which the nef gene is inserted into deletion site III of the MVA viral genome. However, none of the documents, either alone or in combination, teach or even suggest a recombinant MVA virus containing and capable of expressing HIV nef inserted at a site of a naturally occurring deletion within the MVA genome, wherein the site of the naturally occurring deletion is not site III. Accordingly, the cited references, either alone or in combination, would not have suggested the claimed invention to one of ordinary skill in the art, at the time the invention was made, with a reasonable expectation of success.

In summary, as discussed in detail above, the cited references, either alone or in combination, would not have reasonably suggested the claimed invention to one of ordinary skill in the art, at the time the invention was made, with a reasonable expectation of success. The

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cited references merely indicate that isolated elements and/or features recited in the claims are known. This is insufficient to render the claimed invention *prima facie* obvious.

Accordingly, the pending claims are nonobvious over the cited references and their combination(s).

Rejection of Claims 6, 7, 33 and 34 under 35 U.S.C. §103(a)

Claims 6, 7, 33 and 34 are rejected under 35 U.S.C. §103(a) “as being unpatentable over Small Jr. et al. (US Patent 5,676,950) as applied to claims 1-5 and 11 above, and in view of Altenburger (1989 PTO-1449 AZ) and further in view of Kwon (US Patent 5,679,511)” (Office Action, page 10). The Examiner cites Small *et al.* and Altenburger *et al.* as above. The Examiner cites Kwon as disclosing “the cDNA sequence encoding human tyrosinase, and the expression of that protein from bacteriophage vectors” (Office Action, page 11). The Examiner states that “Kwon provides motivation to use the tyrosinase gene as an antigen as it is involved in melanomas, and could be a vaccine antigen” (Office Action, page 11). It is the Examiner’s opinion that”

[i]t would have been obvious for one of ordinary skill in the art at the time the invention was made to have selected any one of the naturally occurring deletion sites of MVA, including site II, for insertion of sequences encoding heterologous antigens. Small Jr. et al. disclose that MVA has six suitable sites for such insertions, and indicate that any site can be utilized. Both Altenburger et al. and Small Jr. et al. disclose that heterologous antigens are efficiently expressed from the insertion sites, and such antigens can provide protection from homologous challenge. Small Jr. et al. disclose the use of recombinant MVA viruses for cancer prevention when the proper cancer antigen is provided. Kwon provides that antigen, human tyrosinase, and indicates it could be used in a melanoma vaccine. One of skill in the art would have been further motivated to use the MVA virus because it is an excellent vaccine candidate due to its extreme attenuation, the availability of insertion sites, the level of gene expression, and the safety for laboratory workers (Office Action, pages 11-12).

Applicants respectfully disagree. The claimed invention relates to a recombinant MVA virus containing and capable of expressing HIV nef or human tyrosinase inserted at a site of a naturally occurring deletion within the MVA genome, wherein the site of the naturally occurring deletion is not site III.

As discussed above, neither Small *et al.* nor Altenburger *et al.* teach or even suggest inserting a heterologous gene in deletion site II of the MVA genome for any purpose. Kwon does not provide what is lacking in the combined teachings of Small *et al.* and Altenburger *et al.*

to render Applicants' claimed invention obvious. Kwon teaches "cDNA clones for human tyrosinase" (Kwon, column 1, line 20). There is no discussion of the MVA virus in the Kwon patent.

A combination of the cited art would at most direct the person of skill in the art to construct a recombinant vaccinia virus which expresses the tyrosinase protein for oral immunization, or construct a recombinant MVA virus in which the tyrosinase gene is inserted into deletion site III of the MVA viral genome. However, none of the documents, either alone or in combination, teach or even suggest a recombinant MVA virus containing and capable of expressing tyrosinase inserted at a site of a naturally occurring deletion within the MVA genome, wherein the site of the naturally occurring deletion is not site III. Accordingly, the cited references, either alone or in combination, would not have suggested the claimed invention to one of ordinary skill in the art, at the time the invention was made, with a reasonable expectation of success.

In summary, as discussed in detail above, the cited references, either alone or in combination, would not have reasonably suggested the claimed invention to one of ordinary skill in the art, at the time the invention was made, with a reasonable expectation of success. The cited references merely indicate that isolated elements and/or features recited in the claims are known. This is insufficient to render the claimed invention *prima facie* obvious.

Accordingly, the pending claims are nonobvious over the cited references and their combination(s).

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (781) 861-6240.

Respectfully submitted,

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